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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,033	07/03/2001	Mark Henry Pausch	011420102	5078

22852 7590 06/14/2005

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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,033	PAUSCH ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-7,9,20-24,28 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-7,9,20-24,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *01 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application: Claims and Amendments

Applicant is notified that the amendments put forth on 1/6/05, have been entered in full. Upon further consideration, the finality of the previous office action is withdrawn. It is noted that a Notice of Appeal and Appeal Brief have been filed. Applicant can request a refund for the associated fees or leave it as credit for future appeals.

Response to Amendment

Applicant is notified that any outstanding objection or rejection that is not expressly maintained in this Office action has been withdrawn in view of Applicant's amendments, persuasive arguments and upon further consideration. Specifically, the rejections under 35 U.S.C. 103 are withdrawn in view of an analysis of the state of the art at the time the invention was made. The instant invention appears to be predicated on the idea that domains known to be involved in mammalian GPCR receptor desensitization and/or internalization are also functional when the mammalian GPCR is expressed in yeast cells, see pages 6, line 26 through page 7, line 6, of the instant specification. As with many mammalian GPCRs, the C-terminal domain of the endogenous yeast GPCR, Ste2p, was known to be required for receptor desensitization and internalization, but how this worked remained a long standing mystery as no obvious yeast homologues of the mammalian desensitization machinery were known, e.g. no GPCR kinases nor arrestins could be found in yeast, see Feng-y et al., Molecular and Cellular Biology, 20(5)563-574)2000, page 2, col. 1, last paragraph. Consequently, one of ordinary skill in the art would not have expected that the desensitization domains of the mammalian GPCRs would be

active when the GPCRs are expressed in yeast. Furthermore, even if yeast homologs of the mammalian desensitization machinery were suspected to exist by one skilled in the art, such an artisan would have a low expectation that those proteins would recognize the mammalian receptors because the interactions between a particular GPCR and its desensitizing proteins are know to be highly substrate-specific.

Thus, while the concept of deleting desensitization domains of yeast and of mammalian GPCRs to increase their sensitivity was well established in the art, as reviewed in the instant specification at pages 7-8 and by Feng et al., the concept of deleting such domains in mammalian GPCRs to increase their sensitivity when expressed in yeast appears to be novel and unobvious at the time the invention was made. Additionally, in the yeast assay described by U.S. Patent No: 5789184, the concept of avoiding desensitization of the pheromone response pathway is disclosed but there is no mention of doing so at the level of the receptor, e.g. by mutating the receptor as in the instant claims, see col 10, lines 44-52 of U.S. Patent No: 5789184.

Maintained Rejections:

Claim 29 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The specification sets forth that "IC3Δ" specifically refers to a third intracellular loop that comprises a deletion such that 22 amino acids proximal to the 5th transmembrane segment remain and are fused to the 22 amino acids proximal to the 6th transmembrane domain, as set forth on page 7 regarding MAR, and page 13 regarding CCKB-receptor, yet the specification

also specifically refers to IC3Δ as a third intracellular loop that comprises a deletion such that 39 amino acids proximal to the 5th transmembrane segment remain and are fused to the 41 amino acids proximal to the 6th transmembrane domain, as set forth on page 16 regarding the Alpha2A adrenergic receptor. Thus, the specification has defined the term "IC3Δ" only by way of various and differing examples – thus the artisan could not unambiguously know whether a particular "IC3Δ" is ***the*** IC3Δ required by claim 29.

Applicant's arguments regarding the erroneous statements of the prior action are well taken yet the issue remains, as discussed above.

New Rejection:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 3, 5, 6, 7, 9, 20-24, 28, 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the genus of yeast cells comprising a heterologous GPCR with a deletion mutation in either the 3rd intracellular loop or the C-terminus that improves the function of the GPCR, wherein the deletion in the 3rd intracellular loop results in a 44 amino acid third intracellular loop comprising the 22 residues proximal to the 5th and the 6th transmembrane domains, does not reasonably provide enablement for the genus of yeast cells comprising a heterologous GPCR with a deletion in an intracellular domain that improves the function of the GPCR, and nor for the specific embodiment of that containing a human alpha2

adrenergic receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As set forth above the specification discloses the concept that domains known to be involved in mammalian GPCR receptor desensitization and/or internalization are also functional when the mammalian GPCR is expressed in yeast cells, see pages 6, line 26 through page 7, line 6, of the instant specification. The specification indicates that deletions can be made to a variety of GPCRs wherein the remaining third intracellular loop comprises the 22 residues proximal to the 5^{th} and the 6^{th} transmembrane domains, resulting in a 44 amino acid third IC loop (e.g. Examples 1-3). This is a very specific teaching, yet the claims encompass any of a practically infinite number of deletions. The specification has not taught a method for the artisan to use to discover other such deletion strategies and has only offered the artisan an invitation to randomly try to find such. The situation in example 4 is quite different, wherein the region to be deleted is found by comparing two SSTRs, one that does function in yeast and the other that does not. This does not appear to be a common occurrence in the art, and the artisan would not consider the disclosure of this single example as providing an adequate teaching to support the claimed genus.

The claims are thus, for the reasons above, in essence single means claim, because the claims encompasses any composition having the recited activities whereas the instant specification only discloses a single composition known to the inventor. In *In re Hyatt*, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983), a single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification at most disclosed only those means known to the inventors.

When claims depend on a recited property, a fact situation comparable to *Hyatt* is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. See also *Fiers v. Sugano*, 984 F.2d 164, 25 USPQ2d 1601 (Fed. Cir. 1993), and MPEP § 2164.08(a). The skilled artisan would not expect to readily find such other deletion mutants. As indicated previously, the prior art demonstrates that many deletions diminish the efficiency G-protein activation – a property that is asserted to be necessary for the instant invention, see page 3 of the instant specification and pg 13 L10-14 of Strader (WO 96/00739) who teaches away from the expectation that such deletions would improve functional coupling of the receptor to the G-protein.

Nor does the specification point-out what other intracellular domains are involved desensitization and/or internalization and nor is this generally known in the art. One skilled in the art appreciates that individual specific receptors may turn-out to include other domains in addition to the IC3 and C-terminal, yet the specification has provided no particular instruction in this regard, nor any guiding principle to use to find such if they can be found. Additionally, claims 1 and 7 specifically require that the GPCR be an alpha2A adrenergic receptor. The specification does not indicate that such deletions improve the function of this receptor, i.e. example 5, and the specification has not taught how to acquire such, as required by the claims.

Therefore, due to the large quantity of experimentation necessary to generate the infinite number of variants required by the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features, other than those known to be involved in receptor desensitization, are required in order to provide activity,

the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which does not recognize intracellular domains other than that of the third loop and C-tail involved in desensitization and by Strader who demonstrates that many deletions diminish the efficiency G-protein activation, and the breadth of the claims which fail to recite any structural limitations, undue experimentation would be required of the skilled artisan to make use the claimed invention in its full scope.

Conclusion

Please note the new central fax number for official correspondence below:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D., can be reached at (571) 272-0829. Official papers filed by fax should be directed to 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

MB

ELIZABETH KEMMERER
PRIMARY EXAMINER

June 6, 2005